FORM PTO-1390 (Modified) (REV 10-95) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR
1348	09/701334

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/DE 99/01541	MAY 26, 1999	MAY 28, 1998

TITLE OF INVENTION

PHARMACEUTICAL PREPARATIONS FOR REGULATING THE RELEASE OF INSULIN BY INFLUENCING THE B-CELL OF THE PANCREATIC ISLETS OF LANGERHANS

APPLICANT(S) FOR DO/EO/US

Elmar PESCHKE, Jan-Dirk FAUTECK, Dorothee PESCHKE, Caterina BORIA, Ulrich MUSSHOFF

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☐ A copy of the International Search Report (PCT/ISA/210).
8. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☐ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 13 to 18 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
    A **SECOND** or **SUBSEQUENT** preliminary amendment.
16. ☐ A substitute specification.
17. ☐ A change of power of attorney and/or address letter.
18. ☒ Certificate of Mailing by Express Mail
19. ☐ Other items or information:

EF 042301797 US

526 Rec'd PCT/PTO 27 NOV 2000

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/701334	PCT/DE 99/01541	1348

20. The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

		CALCULATIONS PTO USE ONLY
☐ Search Report has been prepared by the EPO or JPO	**$930.00**	
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482)	**$720.00**	
☐ No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2))	**$790.00**	
☒ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2) paid to USPTO	**$1,070.00**	
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)	**$98.00**	

ENTER APPROPRIATE BASIC FEE AMOUNT =	**$1,000.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	**$0.00**	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	4 - 20 =	0	x $18.00	**$0.00**	
Independent claims	1 - 3 =	0	x $80.00	**$0.00**	
Multiple Dependent Claims **(check if applicable)**.			☐	**$0.00**	
TOTAL OF ABOVE CALCULATIONS =				**$1,000.00**	
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) **(check if applicable)**.			☐	**$0.00**	
SUBTOTAL =				**$1,000.00**	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +				**$0.00**	
TOTAL NATIONAL FEE =				**$1,000.00**	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).**			☐	**$0.00**	
TOTAL FEES ENCLOSED =				**$1,000.00**	
				Amount to be: refunded	$
				charged	$

☐ A check in the amount of to cover the above fees is enclosed.

☒ Please charge my Deposit Account No. **19-4675** in the amount of **$1,000.00** to cover the above fees.
A duplicate copy of this sheet is enclosed.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **19-4675** A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

STRIKER, STRIKER & STENBY
103 EAST NECK ROAD
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SIGNATURE

MICHAEL J. STRIKER
NAME

27233
REGISTRATION NUMBER

NOVEMBER 27, 2000
DATE

UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner: Group: Attorney Docket # 1348

Applicant(s) : PESCHKE, E., ET AL

Serial No. :

Filed : Simultaneously

For : PHARMACEUTICAL PREPARATIONS FOR REGULATING THE RELEASE OF INSULIN BY INFLUENCING THE β-CELL OF THE PANCREATIC ISLETS OF LANGERHANS

SIMULTANEOUS AMENDMENT

November 27, 2000

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

S I R S:

Simultaneously with filing of the above identified application please amend the same as follows:

In the Claims:

Claim 4 line 1 delete “one of Claims 1 to 3", substitute with “claim 1".

REMARKS:

This Amendment is submitted simultaneously with filing of the above identified application.

With the present Amendment applicant has amended the claims so as to eliminate their multiple dependency.

Consideration and allowance of the present application is most respectfully requested.

Respectfully submitted,

Michael J. Striker
Attorney for Applicant(s)
Reg. No. 27233

Chemical Translations

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PCT/DE 99/01541

Inv.: Peschke, E., et al.

Ref.: 1348

Pharmaceutical Preparations for Regulating the Release of Insulin by Influencing the beta-Cell of the Pancreatic Islets of Langerhans

Translated from the German for
STRIKER, STRIKER & STENBY

PHARMACEUTICAL PREPARATIONS FOR REGULATING THE RELEASE OF INSULIN BY INFLUENCING THE β-CELL OF THE PANCREATIC ISLETS OF LANGERHANS

The invention relates to the use of melatonin and/or the chemically modified derivatives thereof for making pharmaceutical preparations for the regulation of insulin release by influencing the β-cell of the pancreatic islets through a melatonin-specific receptor.

Melatonin (N-acetyl-5-methoxytryptamine), an indolamine, is a hormone of the pineal gland which was also found in the retina, in Harder's gland of rodents and in the enterochromaffin cells. It is used, among other things, to combat insomnia (sedative implications), reduce jet lag problems after intercontinental flights and synchronization problems arising from short-term changes in work schedule (shift work), to protect cells from free radicals (particularly hydroxyl radicals), to retard tumor growth, to prevent cataracts as well as to prolong life (S.F. Pang et al., Recent development of pineal melatonin and its receptors in humans. In: P.L. Tang et al., (eds), Melatonin: A Universal Photoperiodic Signal with Diverse Actions, Front. Horm. Res. 21:133-146, 1996).

Melatonin plays a critical role in the regulation of circadian rhythms. For example, it synchronizes the free-running sleep-wake cycle in blind persons. The photically-controlled neural influx (catecholamine influx) is converted in the pineal gland into a hormonal signal (melatonin). The pineal gland acts as a neuroendocrine "translator" and by increasing nocturnal melatonin secretion provides information about the relationship between the light and the dark periods in the course of the day (clock function) and about its changes in the course of the year (calendar function).

In mammals - in contrast to birds - the regulation of the circadian rhythm, however, does not take place directly in the pineal gland, but in a hypothalamic nuclear region, the suprachiasmatic nuclei (SCN). These nuclei play a critical role as primary "circadian pacemakers" in the generation of circadian rhythms in mammals (S. Reuss, Components and connections of the circadian timing system in mammals, Cell Tissue Res. 285: 353-378, 1996).

Especially important for the understanding of the functional interactions between this hypothalamic nucleus and the pineal gland was the detection of melatonin receptors in SCN indicating a functional interaction between the two structures (V.M. Cassone, Melatonin and suprachiasmatic nucleus. In: D.C. Klein et al. (eds.), Suprachiasmatic nucleus, The mind's clock. Oxford University Press 1991, 309-323).

The fact that, besides a multiplicity of other functional features, the density of melatonin receptors in SCN is increased during the day, whereas in contrast to this, physiological, biochemical and morphological studies have indicated an increase in activity of the pineal gland during the night, is consistent with an inhibitory effect of melatonin on the SCN as a time-related, fine-regulatory instrument (D.R.

Weaver et al., Localization of melatonin receptors in mammalian brain. In: D.C. Klein et al. (eds.), Suprachiasmatic nucleus, the Mind's clock, Oxford University Press 1991, 289-308).

Melatonin receptors were found to be present not only in the SCN, however, but also in the pars tuberalis (L.M. Williams and P.J. Morgan, Demonstration of melatonin-binding sites on the pars tuberalis of the rat, J. Endocrinol. 119: R1-R3, 1998); P.J. Morgan et al., Melatonin receptors in the ovine pars tuberalis: Characterization and autoradiographical localization, J. Neuroendocrinol. 1: 1-4, 1989), in the retina (G. Tosini and M. Menaker, Circadian rhythms in cultured mammalian retina, Science 272: 419-421, 1996), in the cerebellum (J.D. Fauteck et al., The adult human cerebellum as a target of the neuroendocrine system involved in the circadian timing, Neurosci. Lett. 179: 60-64, 1994) and more recently in peripheral tissues and organs such as the stomach, kidneys, lung, heart, testicles and others (S.F. Pang et al., Melatonin receptors in peripheral tissues: A new era of melatonin research, Biol. Signals 2: 177-180, 1993); P.J. Morgan et al., Melatonin receptors: Localization, molecular pharmacology and physiological significance, Neurochem. Int. 24: 101-146, 1994).

The possibility of influencing insulin release via the melatonin receptors in the pancreas, the Langerhans islets or the insulin-producing β-cell has thus far not been described.

At this time, different melatonin receptor subtypes are known, for example Mel_{1a}, Mel_{1b} and Mel_{1c} whose amino acid sequences and membrane structure (seven transmembrane helices) have been analyzed (S.M. Reppert et al., Melatonin receptors step into the light: Cloning and classification of subtypes, TIPS 17: 100-102, 1996). These are G-protein-coupled ($Gi_{i/o}$-coupled) receptors blocked by pertussis toxin (pertussis-sensitive G-protein). In view of these relationships, functional melatonin-receptor detections are based on, among other things, the possibility of limiting or abolishing the melatonin-induced inhibition of the forskolin-stimulated increase in cAMP by pertussis toxin (L.L. Carlson, D.R. Weaver and S.M. Reppert, Melatonin signal transduction in hamster brain: Inhibition of adenylyl cyclase by a pertussis toxin-sensitive G protein, Endocrinology 125: 2670-2676, 1989; L.L. Carlson et al., Melatonin receptors couple through a cholera toxin-sensitive mechanism to inhibit cyclic AMP in the ovine pituitary, J. Neuroendocrinol. 7: 361-369, 1995). In summary, it can be stated that in mammals the melatonin-induced inhibition of adenylate cyclase takes place through a pertussis-sensitive G-protein.

The object of the invention is to provide pharmaceutical preparations for regulating the release of insulin by influencing the β-cell of the pancreatic islets through specific receptors.

According to the invention, this objective is reached by use of melatonin and/or a chemically modified derivative thereof to make pharmaceutical preparations capable of regulating the release of insulin by influencing the β-cell of the pancreatic islets through a melatonin-specific receptor.

Surprisingly, we have now found that

- melatonin and/or chemically modified derivatives thereof realize their insulin-reducing influence through G protein-coupled membrane-bound receptors;
- through the melatonin receptor, melatonin and/or its chemically modified derivatives assume pacemaker significance, because the release of insulin from isolated pancreatic islets is at the base of circadian and ultradian rhythms;
- through the melatonin receptor, melatonin and/or chemically modified derivatives thereof in both pharmacological (5 μM) and physiological doses (0.2 nM) significantly reduce the stimulated insulin release from pancreatic islets.

Another object of the present invention are pharmaceutical preparations for oral and parenteral, including topical, rectal, subcutaneous, intravenous, intramuscular, intraperitoneal, intranasal, intravaginal, intrabuccal or sublingual, administration which besides the usual carriers and diluents contain as the active ingredient a compound claimed in Claim 1.

Suitable pharmaceutical formulations are the following:

- tablets, capsules or coated tablets with 0.01 to 200 mg of active ingredient, used orally,
- ampules with 0.01 to 200 mg of active ingredient, for subcutaneous injection,
- adhesive tape with transdermal release of 0.01 to 200 mg of active ingredient,
- subcutaneous implants with a release capacity of 0.01 to 200 mg of active ingredient,
- gels and creams with transdermal release of 0.01 to 200 mg of active ingredient,
- buccally administered systems releasing 0.01 to 200 mg of active ingredient.

The drugs of the invention are prepared in appropriate doses in the known manner with conventional solid or liquid carriers or diluents and conventional pharmaceutical-technical auxiliary agents, in accordance with the desired type of administration.

FUNCTIONAL DEMONSTRATION OF MEMBRANE-BOUND MELATONIN RECEPTORS OF THE PANCREATIC ISLET

Fig. 1 shows a graphic representation of the statistically significant drop in glucose-stimulated and KCl-stimulated insulin secretion, induced by melatonin (MT, here 5 μM) - nutrient solution containing glucose or KCl + melatonin = dark bars, in comparison with a control - nutrient solution containing glucose or KCl = light bars.

The results are statistically significant with a probability of error $p < 0.001$.

Fig. 2 shows the influence of melatonin (here 10 nM melatonin) on the forskolin-stimulated release of insulin brought about by increasing concentrations of forskolin.

The insulin-reducing influence of melatonin is significant.

It can be seen from both figures that melatonin in physiological as well as pharmacological doses reduces KCl-stimulated, glucose-stimulated and forskolin-stimulated insulin secretion. This is due to inhibition of voltage-dependent Ca^{2+} channels and/or of adenylate cyclase. Moreover, it was demonstrated in phase-response studies that melatonin, used as pacemaker, brings about a phase acceleration of circadian insulin secretion.

FUNCTIONAL DEMONSTRATION OF MEMBRANE-BOUND MELATONIN RECEPTORS OF PANCREATIC ISLETS BY USE OF GTPγS (guanosine S [gamma-thio]triphosphate)

Fig. 3 shows the influence of non-hydrolyzable GTPγS on the action of melatonin.

A comparison of data obtained for a nutrient solution containing melatonin + forskolin with a solution consisting of the nutrient solution containing melatonin + forskolin + GTPγS shows that the action of melatonin on the forskolin-stimulated release of insulin is nearly abolished by GTPγS. The reason for this is the functional blockade of the melatonin receptors by GTPγS.

These results can be interpreted as direct evidence of receptor-specific regulation of insulin release, and this for the first time constitutes proof of the existence of a functional melatonin receptor on the LANGERHANS islet.

AUTORADIOGRAPHIC DETECTION OF MEMBRANE-BOUND MELATONIN RECEPTORS OF THE PANCREATIC ISLET USING 2-$^{(125J)}$IODOMELATONIN

Fig. 4 shows an autoradiographic study of the detection of melatonin receptors on pancreatic tissue (frozen section) of neonatal rats.

The punctiform signals represent binding sites of 2-$^{(125J)}$iodomelatonin on the frozen section.

The controls show no punctiform signals.

For exact localization, the developed film plates are shown alone as well as after micromanipulation with the film plates mounted above the tissue photographed at the same time (insert bar: 400 μm).

Fig. 5 shows the quantification of the autoradiographic detection of melatonin receptors as a displacement curve reflecting the displacement of 2-$^{(125J)}$iodomelatonin from its receptor bonds by

noniodinated melatonin. The study was made by computer-assisted gray scale analysis (Optimas 2.0).

These results can be interpreted as direct evidence of the existence of melatonin-specific receptors in the LANGERHANS islet.

MOLECULAR-BIOLOGICAL DETECTION OF MEMBRANE-BOUND MELATONIN RECEPTORS OF THE PANCREATIC ISLET

Fig. 6 shows the amplified PCR product which has a length of 329 bp and represents a specific partial sequence of the melatonin receptor sequence. In this manner, the melatonin receptors in the LANGERHANS islet were detected for the first time on a molecular level.

The exact methodology of molecular-biological detection is described in the following.

1. Preparation of the Pancreatic Tissue

The pancreatic tissue used for the molecular-biological study was obtained from eight neonatal rats (male and female) and stored at -70 °C until needed for further study.

2. RNA Extraction

Total RNA was isolated from 150 mg of pancreatic tissue by the guanidine thiocyanate/LiCl method of Cathala et al., A method of isolation of intact translationally active ribonucleic acid, DNA: 329-335, 1983.

The purity and quantity of the isolated RNA were determined by photometric absorption measurement.

The quantity of isolated RNA was 150 μg.

The ratio of optical density (O.D.) at 260 nm to that at 280 nm was 1.7.

3. Establishment of a cDNA Library by Reverse Transcriptase Reaction (RT)

In the RT reaction, mRNA is reversely transcribed into complementary DNA (copy DNA, cDNA) which then serves as the starting matrix for the subsequent amplification (PCR reaction).

The cDNA synthesis was carried out according to directions provided by the manufacturer of the corresponding kit (Pharmacia-Biotech). 5 μg of RNA was used as matrix for the RT reaction.
The incubation was carried out at 37 °C for 60 minutes.

4. Polymerase Chain Reaction (PCR)

The molecular-biological detection of the transcription products for the Mel_{1A} receptor was carried out by use of the PCR technique. To this end, partial sequences of the cDNA molecules of the melatonin receptors were amplified with the aid of specific oligonucleotide sequences (primers).

The resulting PCR products were detected on conventional agarose gels.

In constructing the primers, both the length (base pairs) and base composition (G/C content) of the primers and the length of the PCR products were taken into account as required by rules.

The primers were specific for a partial cDNA fragment of the rat melatonin receptor according to Reppert et al., Cloning and characterization of a mammalian melatonin receptor that mediates reproductive and circadian responses, Neuron 13: 1177-1185, 1994; cf. Accession No.: U14409.

The position of the primers covers the cDNA regions 11-33 (up primer) and 319-339 (low primer). The specific PCR product should have a length of 329 bp.

The conditions for PCR were as follows: 94 °C (1 min) - 55 °C (1 min) - 72 °C (1 min), and at the end 15 min at 72 °C.

Forty cycles were carried out.

The PCR product was investigated electrophoretically in a 2.5% agarose gel (plus ethidium bromide). The length standard was a 100 bp DNA standard.

Running time was 90 min at 50 volts in a standard electrophoresis buffer.

PATENT CLAIMS

1. Use of melatonin and/or of a chemically modified derivative thereof for making pharmaceutical preparations for the regulation of insulin release by influencing the β-cell of the pancreatic islets through a melatonin-specific receptor.

2. Use of melatonin and/or of a chemically modified derivative thereof according to Claim 1, characterized in that the regulating action consists of inhibiting insulin release.

3. Use according to Claim 1 for treating hyperinsulinemia.

4. Use according to at least one of Claims 1 to 3, characterized in that the pharmaceutical preparation is made in the form of tablets, capsules, coated tablets, transdermal therapy systems, ampules, suppositories, gels, ointments, implants or buccally administered systems.

SUMMARY

The present invention relates to the use of melatonin and/or a chemically modified derivative thereof for making pharmaceutical preparations for the regulation of insulin release by influencing the β-cell of the pancreatic islets through a melatonin-specific receptor.

Surprisingly, we have found that melatonin and/or chemically modified derivatives thereof, when used according to the invention,

- realize their insulin-reducing influence through G- protein-coupled membrane-bound receptors;
- through the melatonin receptor assume pacemaker significance, because the release of insulin from isolated pancreatic islets underlies the circadian and ultradian rhythms;
- through the melatonin receptor, in pharmacological (5 μm) as well as in physiological doses (0.2 nm), reduce the stimulated release of insulin from pancreatic islets in statistically significant manner.

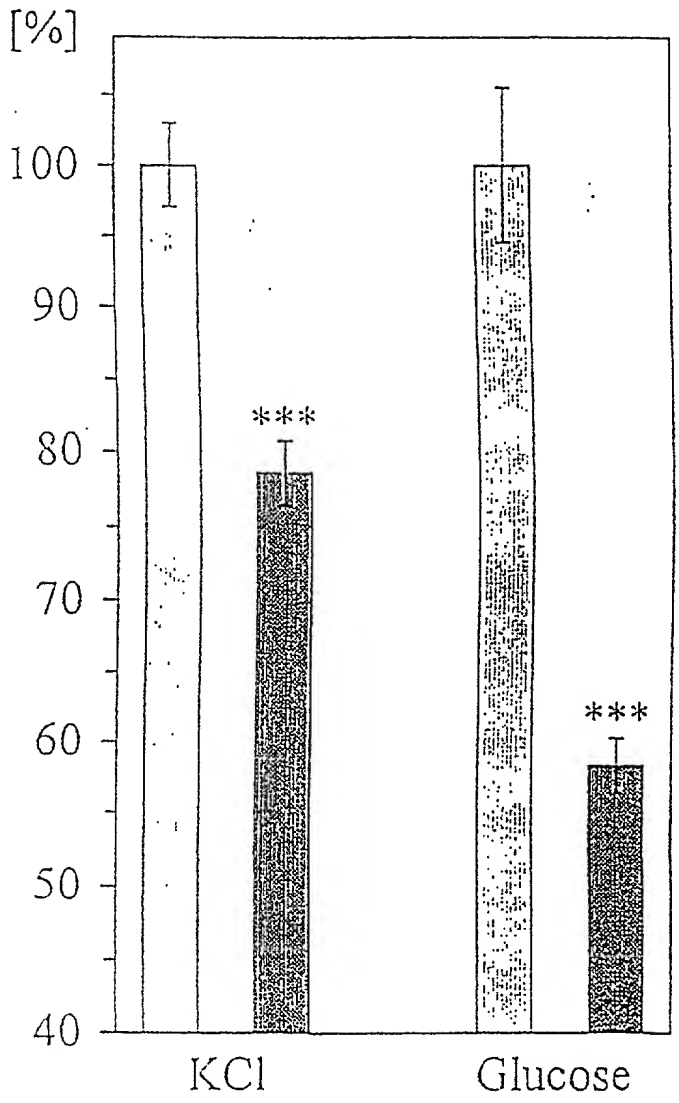

Figure 1

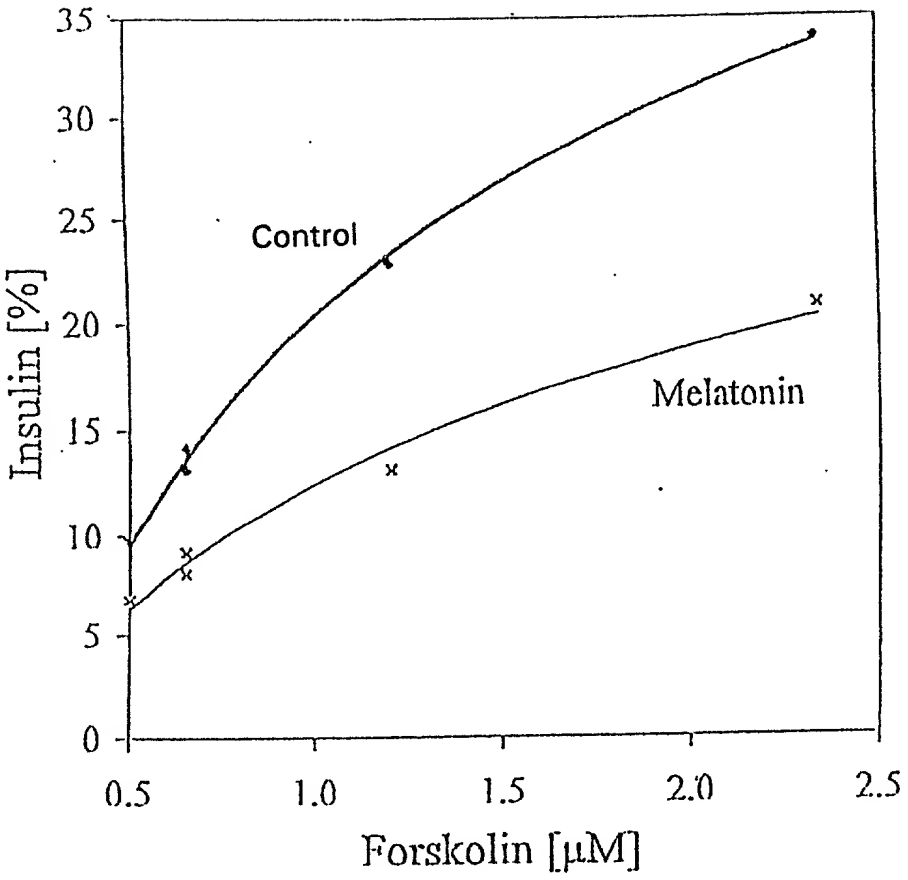
35
30
25
20
15
10
5
0
Insulin [%]
Control
Melatonin
0.5
1.0
1.5
2.0
2.5
Forskolin [μM]

Figure 2

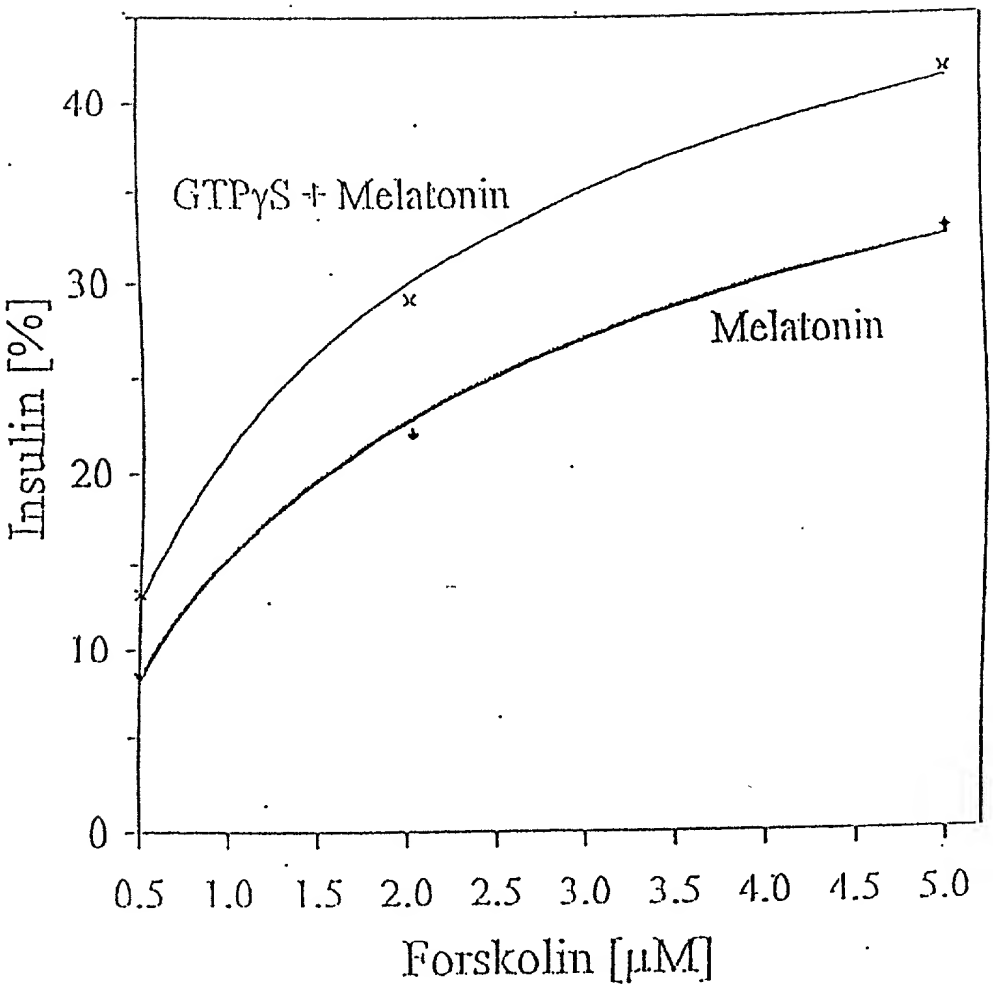
40
30
20
10
0
Insulin [%]
GTPγS + Melatonin
Melatonin
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
Forskolin [μM]

Figure 3

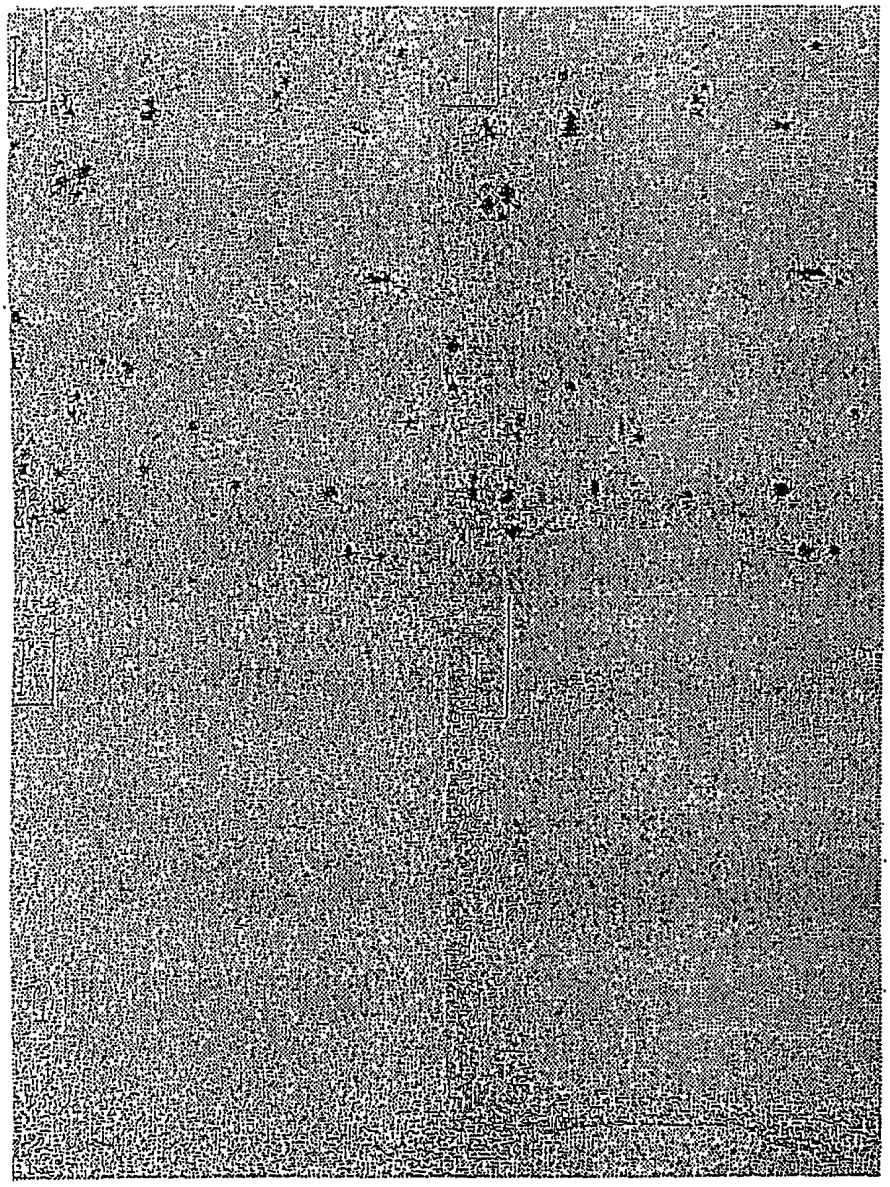

Figure 4

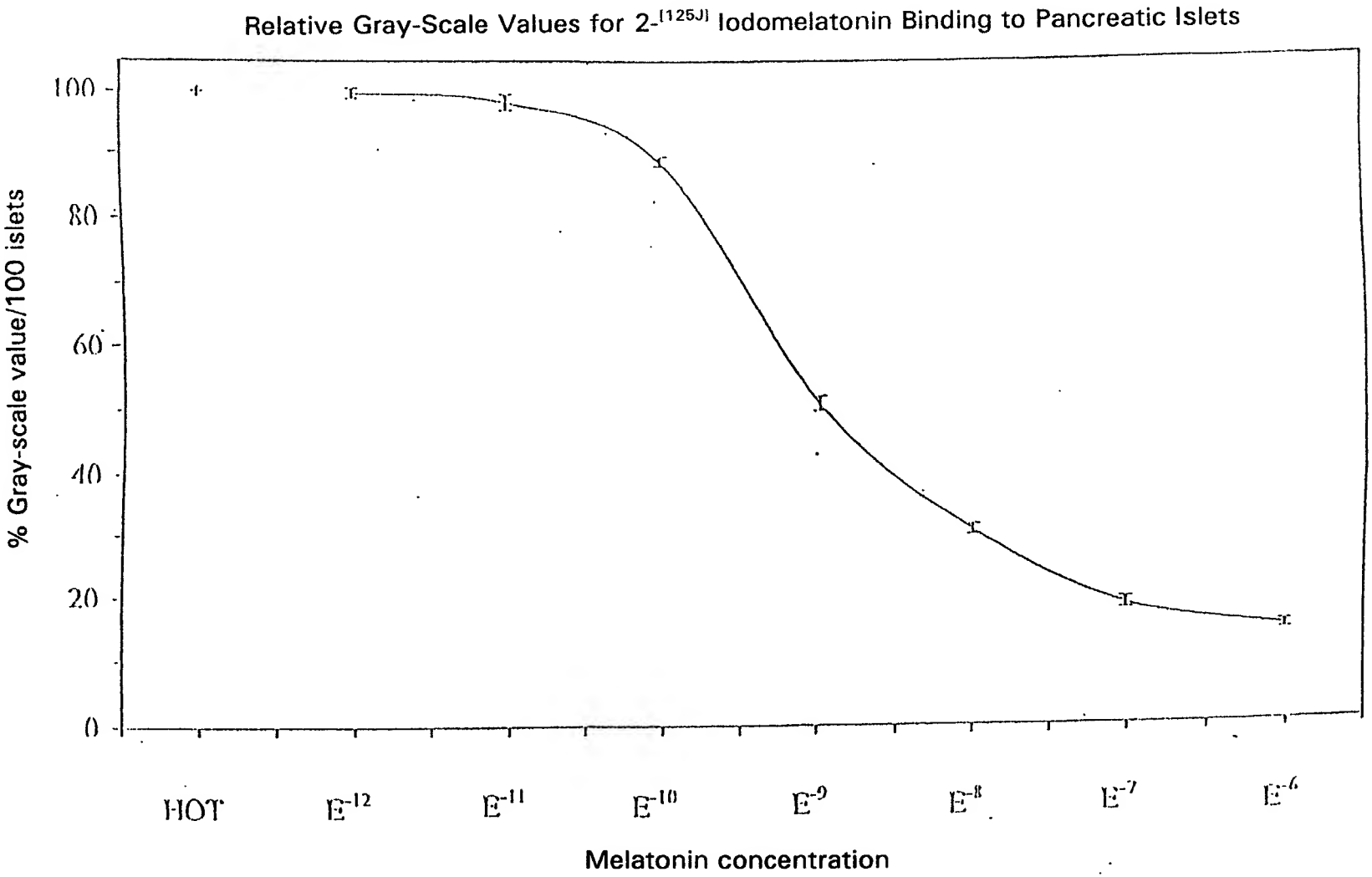

Figure 5

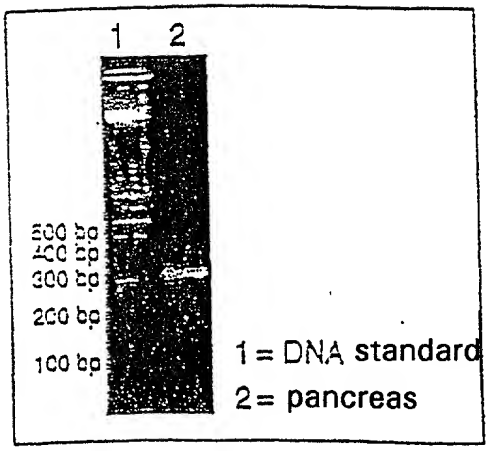

Figure 6

DECLARATION AND POWER OF ATTORNEY FOR NATIONAL STAGE OF PCT PATENT APPLICATION

As a below-named inventor, I hereby declare that:

Elmar PESCHKE
Jan-Dirk FAUTECK
Dorothee PESCHKE
Caterina BORIA
Ulrich MUSSHOFF

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled **PHARMACEUTICAL PREPARATIONS FOR REGULATING THE RELEASE OF INSULIN BY INFLUENCING THE β-CELL OF THE PANCREATIC ISLETS OF LANGERHANS** the specification of which was filed as PCT International Application number PCT/DE 99/01541 on May 26, 1999.

I hereby state that I believe the named inventor or inventors in this Declaration to be the original and first inventor or inventors of the subject matter which is claimed and for which a patent is sought.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose all information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

Prior foreign application(s):			Priority claimed:	
198 23 829.0	GERMANY	MAY 28, 1998	X	
(Number)	(Country)	(Date filed)	Yes	No
(Number)	(Country)	(Date filed)	Yes	No

As a named inventor, I hereby appoint the following attorney to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Michael J. Striker, Reg. No. 27233

Direct all telephone calls to Striker, Striker & Stenby at telephone no.: (631) 549 4700 and address and all correspondence to:

STRIKER, STRIKER & STENBY
103 East Neck Road
Huntington, New York 11743
U.S.A.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statement

may jeopardize the validity of the application or any patent issued thereon.

Signature: Elmar Peschke	Date: 22.XI.2000	Residence and Full Postal Address: Hoher Weg 11 D-06120 Halle DEX Germany
Full Name of First or Sole Inventor: Elmar PESCHKE	Citizenship: GERMAN	
Signature: Jan-Dirk Fauteck	Date: 23.11.00	Residence and Full Postal Address: August-Bebel-Strasse 27a D-07743 Jena DEX Germany
Full Name of Second Inventor: Jan-Dirk FAUTECK	Citizenship: GERMAN	
Signature: Dorothee Peschke	Date: 22.11.2000	Residence and Full Postal Address: Hoher Weg 11 D-06120 Halle DEX Germany
Full Name of Third Inventor: Dorothee PESCHKE	Citizenship: GERMAN	
Signature: Caterina Boria	Date: 16.11.00	Residence and Full Postal Address: Via Catalani, 75 I-20131 Milano ITX Italy
Full Name of Fourth Inventor: Caterina BORIA	Citizenship: ITALIAN	
Signature: Ulrich Musshoff	Date: 27.11.00	Residence and Full Postal Address: Auf dem Draun 88 D-48149 Muenster Germany
Full Name of Fifth Inventor: Ulrich MUSSHOFF	Citizenship: GERMAN	
Signature:	Date:	Residence and Full Postal Address:
Full Name of Sixth Inventor:	Citizenship:	
Signature:	Date:	Residence and Full Postal Address:
Full Name of Seventh Inventor:	Citizenship:	
Signature:	Date:	Residence and Full Postal Address:
Full Name of Eighth Inventor:	Citizenship:	